REMARKS

Claims 51-61 are pending. These replace claims 39-47, 49 and 50 presented previously . Claim 48 has been cancelled, in order to expedite prosecution. It has not been cancelled out of agreement with the examiner's position. In view of this, the issue raised at point 8 of the office action is moot.

There was no PTO-948 attached to the office action. Applicants cannot address a document that has not been received.

With respect to point 4, "hybridizes" has been corrected; however, the remainder of the objection is obscure.

Points 5 and 6 do not require comment.

In point 7, the examiner rejected all of claims 39-50 under 35 USC § 112, first paragraph. According to the examiner, "the conditions recited in the claims are not supported by data in the specification." The examiner then cites to what are clearly typographical errors. (Perhaps this is what was intended in point 4, but this is not clear). The examiner then objects to what is standard technological usage, i.e., the use of a backslash, and asserts that this means division! The basis for this reading of the claims is not clear. In the replacement claims, the standard nomenclature is not used in deference to the examiner. The examiner also states that "the specification recites multiple washing steps in the alternative; however, the claims recite all washing steps as consecutive.

The specification actually teaches both. Page 40 is certainly relevant, but applicants have also pointed to page 6, lines 30-35 of the specification. The examiner has ignored this.

Turning to the rejection at point 9, the examiner just states that "neither the specification nor the claims teach how to define the variables G, H, Y or W, as recited within the sequences."

It is suggested that the examiner review 37 CFR § 1.822(b), as well as MPEP 2422, page 2400-22. The nomenclature applicants used is that which is required by the USPTO. The issue raised as to "G" is especially obscure, since the four standard nucleotides are represented by "a, t, c and g." Given that applicants have followed the very specific rules set out by the MPEP and 37 CFR it is not at all understood why applicants are now being advised that they do not support this language and usage.

The examiner then cites to boilerplate, including Vas-Cath, Inc. v. Mahurkar, 19 USPQ 2d 1111, Fiers v. Revel, Anigen, Inc. v. Chugai Pharmaceuticals Co. Ltd. ((NOT "Lts" as recited).

First, with respect to the examiner's statement that the skilled artisan cannot envision the detailed structure of the encompassed nucleic acid molecules because the variables have not been defined," it is suggested that MPEP 2422 be reviewed. Further, in both Fiers and Anigen, the factual situation was that NO species recited within the claims had been disclosed. With respect to the citation to Reagents of the University of California v. Eli Lilly, the examiner expressly admits that "the description of a genus is achieved by the recitation of a representative number of SEQ ID NO'S falling within the scope of the claimed genus." Applicants have pointed out previously that nearly 500 oligonucleotides are described which fall within the genus. How many more would the examiner suggest be disclosed.

It is pointed out that, during a telefonic interview - record of which has NOT been made by the examiner - applicants were told, specifically, that if this written description rejection were to be maintained, a biotechnology patent specialist would be consulted, and a follow up interview would be scheduled. Whether a biotechnology specialist was consulted is not clear from the record; however, there was no follow up interview scheduled. AS SUCH, APPLICANTS NOW INSIST THAT SUCH AN INTERVIEW BE SCHEDULES IF THIS REJECTION BE MAINTAINED.

With respect to the rejection under 35 USC § 112, first paragraph, the examiner states:

> "Many nucleic acids that hybridize to a transcript of the gene will not be an indicator of a human polypeptide having PI3 kinase activity and a molecular weight of about 110kD as determined by SDS-PAGE."

The claims do not call for identification of a human polypeptide. The claims call for determining expression of a gene. The first step in expression is formation of transcript. Specific conditions are recited in the claims. The claim is presumed enabled. The burden is on the examiner to show why there is no enablement. Federal Circuit precedent specifically states that generic statements, not supported by factual evidence, will not suffice. The examiner has adduced no factual evidence.

The examiner goes on to state:

> "Neither does hybridization determine whether a cell contains a gene which encodes a human polypeptide which has PI3 kinase activity and have a molecular weight of 110kD as determined by SDS-PAGE."

Since the claims do not call for "determination of a gene," the rejection is not understood. In any event, if transcript is present, a gene must be present. Again, the examiner provides no support for the blanket statements.

With respect to the rejection of point 11, the examiner states that "claims 39, 47 and 48 broadly recite any nucleic acid molecule since the nucleic acid molecule is not defined by a particular sequence."

Yet again, applicants expressly call upon the examiner to show where a statute, rule or regulation requires this. Further it is pointed out that the USPTO's own guidelines for determining written description compliance permit the use of the language employed. As to the allegation that claims 44 and 45 recite undefined variables, the examiner is again referred to MPEP 2422.

In point 12, the examiner states that the claims delete essential steps. The examiner states that "there is no contact step," "no detection step" and "no correlation step which correlates the detection to the method of determining expression of the gene."

This rejection is based in an incorrect statement of facts. The first word in claim 51 following "comprising" is --contacting--. In the last line of the claim, applicants call for "determining hybridization as a determination of expression." Hence, the examiner is absolutely incorrect on the statements that are allegedly missing.

The facts are the following. A sample may, or may not, contain transcript of the recited gene. In order to determine whether or not the transcript is present, they contact the sample with a defined nucleic acid molecule at defined conditions. I the transcript is present, the nucleic acid molecule will hybridize to it. Hybridization is determinable via standard, art recognized methods. If the transcript is not present there will not be hybridization. The techniques involved are not all that complex to one of ordinary skill in the art, and they do recite what is required, notwithstanding point "12" of the office action.

In view of the foregoing, the rejection set forth in point "12" of the office action should be withdrawn.

The examiner has rejected all claims 39-47 and 49-50 under 35 USC § 103 over Skolnick in view of Carpenter. Again, the rejection is traversed.

The examiner argues that:

> "(N)o more than routine skill would have been required to use the 110kD protein as taught by Carpenter, *et al.*, instead of the 85kD protein of Skolnick, *et al.*

First, the rejection is confusing. Using "proteins" in an assay does not lead to using DNA. This has been pointed out previously. The invention is an assay method whereby nucleic acid molecules hybridize to a target, i.e., transcript of human PI3 kinase. Note that the claims all relate to "A method for determining a human polypeptide that has PI3 kinase activity and a molecular weight of about 110 kilodaltors as determined by SDS-PAGE." Carpenter very clearly, and unequivocally, does not deal with human material. Note the title: "urification and Characterization of Phosphoienostide 3-kinase from rate liver." There is no suggestion in this reference that the human form is also 110 kilodaltors. There is no teaching of a nucleic acid molecule for the rat protein. It has long been settled that a protein does not render nucleic acid molecules encoding the protein obvious. The examiner's attention is directed to In re Devel in this regard.

The examiner states that "no more than routine skill would have been required to have used the 110kD protein as taught by Carpenter, *et al.* instead of the 85kD protein of Skolnick, *et al.*" One asks -- to do what? Apparently, the examiner would substitute the rat gene of Carpenter into the assay method taught by Skolnick. Why would one do so? Contrary to the examiner's assertion that:

> "Skolnick, *et al.* teaches the cloning of PI3 kinase."

Skolnick teaches cloning of a protein that is associated with PI3 kinase. Note page 84, column 1:

> "GRB-1 encodes the human homolog of PI3 kinase-associated proteins."

How one gets from this to DNA encoding PI3 kinase is not at all clear from the examiner's action. The examiner states that "The GRB-1 protein encodes the human counterpart of PI3 kinase-associated protein which uses a polypeptide that has PI-3 kinase activity." The intent of this statement is unclear. The p85 protein interacts with PI3 kinase, but how does one secure the DNA for PI3 kinase from this protein/protein interaction? The rejection is void of any such explanation.

It is submitted that the rejection under 35 USC § 103 fails to satisfy the minimum requirements of the statute, and as such cannot be maintained.

Withdrawal of the rejection, and all other rejections, is believed proper and is urged.

Respectfully submitted,

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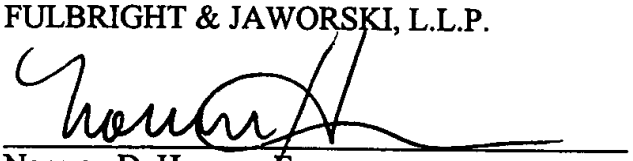

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FULBRIGHT & JAWORSKI LLP

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	:	Hiles, et al.
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For	:	METHODS FOR DETERMINING EXPRESSION OF A P13 KINASE GENE
Art Unit	:	1645
Examiner	:	J. Hines

December 17, 2001

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

SHOWING OF CHANGES

IN THE SPECIFICATION

Page 38, lines 21-38:

The unamplified SGBAF-1 cDNA library (10^6 recombinants) was plated on E.coli K12 PLK-F' (Stratagene) at a density of 10^5 plaques per 15 cm dish and lifts taken in duplicate onto nitrocellulose membranes (Millipore). For screening, filters were prehybridized for at least 1 h at 42^0C in 6 x SSPE, 0.5% SDS, 10 x Denhardt's solution, 100 μg ml^{-1} denatured sonicated herring sperm DNA (Sigma). Hybridization was carried out in the same solution containing 10 ng ml^{-1} radiolabelled oligonucleotide. Oligonucleotides used were: Peptide N (MDWIFHT) (SEQ ID NO: 11) 5'-AA(G/A)ATTGGA(T/C)TGGAT(C/T/A)TT(T/C)CA(T/C)AC-3') (SEQ ID NO: 12); Peptide J(D D G Q L F H I D F G H F) (SEQ ID NO: 13); 5'-GATGATGGCCA(G/A)CTGTT(T/C)CA(T/C)AT(T/A)GA(T/C)TTTGGCCA(T/C)T T (SEQ ID NO: 14). Oligonucleotides were labelled with ^{32}P at the 5' end in a 20 μl reaction containing 100 ng oligonucleotide, 1 x kinase buffer (Promega), 0.1 mM spermidine, 5 mM dithiothreitol, 100 μCi [γ-^{32}P]ATP (5000 Ci $mmol^{-1}$, Amersham) and 2 μl (200 U) 54 polynucleotide kinase (Amersham). Filters

Page 39, lines 18-38:

RACE PCR was carried out essentially as published previously (Frohman, et al., 1988; Harvey and Garlison, 1991). Briefly, first strand cDNA primed with random hexamers (Amersham) was synthesized from 1 μg of SGBAF-1 cell mRNA using the Stratagene first strand cDNA synthesis kit. First strand cDNA was isolated by isopropanol precipitation and tailed with oligo-dA using terminal deoxynucleotidyl transferase (BRL). PCR was performed using oligo 2224 (5'-AATTCACACACTGGCATGCCGAT) (SEQ ID NO: 15) and adaptor-dT (5'-GACTCGAGTCGACATCGATTTTTTTTTTTTTTTT) (SEQ ID NO: 16) as primers using a Perkin Elmer/Cetus Tap polymerase PCR kit (conditions: 94°C 1 min, 35°C 1 min, 72°C 2 min, 30 cycles). Products were fractionated on a 1.5% low melting point agarose gel and visualized by staining with ethidium bromide. The gel was sliced into 6 bands (size range 150-2000 bp) and DNA isolated from each gel slice. A further round of PCR 2 was performed on this DNA using oligonucleotide 2280 (5' –TTTAAGCTTAGGCATTCTAAAGTCACTATCATCCC) (SEQ ID NO: 17) and adaptor (5'-GACTCGAGTCGACATCGA) (SEQ ID NO: 18) as primers (conditions: 94°C 1 min, 56 °C 1 min, 72°C min, 356 cycles. Products were fractioned on an agarose gel and visualized by staining with ethidium.

Page 41, lines 12-35:

For p85α 125 ng of poly $(A)^+$ RNA was reverse transcribed with 2.5 units rTth DNA polymerase (Perkin-Elmer-Cetus) at 70°C for 10 min in a 10 μl reaction containing 10 mM Tris-HCl (pH 8.3), 90 mM KCl, 1mM MnCl, 0.5 mM dNPT mixture and 1.2 μM antisense primer (5'-CAGGCCTGGCTTCCTGT) (SEQ ID NO: 19). For DNA polymerization the reaction volume was adjusted to 50 μl by adding a single mix giving the following final concentrations: 5% (v/v) glycerol, 10 mM Tris-HCl (pH 8.3), 100 mM KCl, 0.75 mM EGTA, 0.05% (v/v) Tween 20, 2 mM $MgCl_2$, 0.24 μM sense primer (5'-AACCAGGCTCAACTGTT) (SEQ ID NO: 20). PCR was then performed under the following reaction conditions: 92°C 1 min, 58°C 1 min, 72°C 1 min for 25 cycles on a Perkin Elmer-Cetus DNA thermal cycler.

Conditions for p110 were similar except concentration of the antisense primer (5'-TGCTGTAAATTCTAAATGCTG) (SEQ ID NO: 21) was increased to 4.8 μM during the reverse transcription step. DNA polymerisation conditions were the same except the final $MgCl_2$ concentration was increased to 2.5 mM and both primers (sense primer = 5'-GTATTTCATGAAACAAATGA) (SEQ ID NO: 22) were present at a final concentration of 0.96 μM. Taq DNA ploymerase (Promega) was also added at 0.03 U μl^{-1} . PCR was performed as follows: 92°C 30 sec, 54°C 5 sec, 72°C 30 sec for 35 cycles. 20 μl of each reaction was run on a 3% agarose gel (Maniatis, et al. 1982) and visualised by staining with ethidium bromide.

Page 42, lines 1-10:

peptide CKMDWIFHTIKQHALN (SEQ ID NO: 23) was synthesized by FMOC chemistry and purified by HPLC. It was then coupled to KLH using glutaraldehyde, and injected into the lymph nodes of rabbits using methods described in Kypta, R M et al., (1990), Cell 62, 481-492. Positive antisera as determined by enzyme-linked immunoassay were affinity purified on specific peptide-Actigel affinity columns. Anti-p85α (Otsu, et al., 1991) and anti CSF-1 receptor (Ashmun, et al., 1989) antisera are previously documented. Immunoprecipitations were carried out as described in Otsu, et al., 1991.

Page 52, lines 26-38 :

The human cDNA was isolated from a cDNA library, made from mRNA isolated from the human cell line KG1a using standard techniques. The probe was a partial cDNA from the second half of the bovine p110 cDNA. The probe was labelled with ^{32}P and hybridised overnight to the library filters at 65^{O}C in 1M NaPi, 7% SDS buffer. The filters were washed in 2xSSC at 50^{O}C, and exposed to X-ray film at -70^{O}C. The nucleotide sequence is shown in Figure 16 together with the corresponding amino acid sequence. The human p110 sequence has 95% homology to the bovine p119 sequence at the DNA level and is 98% identical at the protein level (Figures 17 and 18). The protein sequence is shown in Figure 19. Primers (357) AAG GAT CAG AAC AAT GCC T (SEQ ID NO: 24) and (416) AGG CTT TCT TTA GCC ATC A (SEQ ID NO: 25) were

Page 53, lines 5-23:

Two novel cDNAs related to p110 have been cloned. Degenerate primers were designed to conserved sequences between human p110 and the related yeast gene VPS34 (Sense (GDDLRQD) (SEQ ID NO: 26) 5' GGN GAT/C GAT/C T/C TA/G CGN CAA/G GA-3 (SEQ ID NO: 27) antisense (FHIDFGHF) (SEQ ID NO: 28) 5' A/GAA A/GTG ICC A/GAA A/GTC A/G/TAT A/GTG A/GAA-3) (SEQ ID NO: 29). These were used in RT-PCR reactions using mRNA from the human cell lines MOLT4 and U937 (94^{O}C 30 sec, 50^{O}C 30 sec, 74^{O}C 30 sec for 35 cycles). Two novel cDNA's, PITR-c and PITR-f, related to p110, were isolated. The PITR-c nucleotide sequence is shown in Figure 20. This gene is highly related to the yeast gene VPS34, the VPS34 protein is involved in the protein sorting from the golgi to the vacuole and has an intrinsic PI3-kinase activity. The PITR-f nucleotide sequence is shown in Figure 21 and is more similar to p119 than PITR-c and is likely also to possess PI3-kinase activity. The

alignment of human p110, the human PI3-kinase related genes PITR-c and PITR-f and the yeast PI3-kinase VPS34 are shown in Figure 22. The amino acids conserved in 3 or more of the proteins are shown in the upper case.

Respectfully submitted,

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